REMARKS

Claims 3, 9-17, 25, 26, and 28-38 were pending in the application as of the issuance of the Office Action. In the Amendments to the claims spanning pages 2-7 of this paper, claims 3 and 36-37 have been amended, claims 35 and 38 have been cancelled without prejudice and new claims 39-42 have been added. Accordingly, after the amendments presented herein have been entered, claims 3, 9-17, 25, 26, 28-34, 36-37 and 39-42 will remain pending in this application.

Support for the amendments to the claims and for the new claims may be found throughout the specification and in the claims as originally filed. Specifically, support for the amendments to claims 3(c) and 3(d) and for new claim 40 can be found in the specification at, for example, page 30, line 27 to page 31, line 7, page 26, lines 28-36, and page 1 of Table 1. Support for the amendments to claim 3(e) can be found at, for example, page 32, lines 32-34 and page 26, lines 28-36 of the specification. Support for the amendments to claims 3(f), 3(g) and 37, and new claims 3(h) and 3(i) can be found in the specification at, for example, page 27, lines 34-36, page 30, line 27 to page 31, line 7, and page 1 of Table 1. Support for the amendments to claim 3(j) can be found in the specification at, for example, page 32, lines 32-34, page 27, lines 34-36, page 30, line 27 to page 31, line 7, and page 1 of Table 1. Support for the amendments to claim 36 and new claims 41 and 42 can be found at, for example, page 26, lines 28-36 of the specification. Lastly, support for new claim 39 can be found at, for example, page 26, lines 28-36 and at page 44, lines 1-3 of the specification.

No new matter has been added by the claim amendments or the new claims presented herein. The amendments to the claims should not be construed as an acquiescence to the validity of the Examiner's rejections and were done solely in the interest of expediting prosecution and allowance of the claims. Applicants reserve the right to pursue the claims as originally filed in one or more further applications.

Rejection of Claims 3, 9-17, 25, 26, 28-34 and 36-38 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 3, 9-17, 25, 26, 28-34 and 36-38 under 35 U.S.C. § 112, second paragraph, as allegedly "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention."

With respect to previously numbered claim 3(f), the Examiner is of the opinion that it is unclear which fragment of at least 15 contiguous nucleotides of SEQ

ID NO:1 encodes a polypeptide having a UDP-N-Acetylmuramate-Alanine-Ligase activity. Applicants respectfully traverse this rejection on the grounds that, based on the teachings in Applicants' specification as well as the general knowledge available in the art at the time of filing of the present application, one of skill in the art would find claim 3(f) to be clear and definite. Notwithstanding the foregoing, solely in the interest of expediting examination and in no way acquiescing to the validity of the Examiner's rejections, Applicants have cancelled previously numbered claims 3(f) and 3(g), thereby rendering rejection of these claims moot.

The Examiner has further rejected claim 38, alleging that "it is unclear which region of SEQ ID NO:1 constitutes the modified regulatory region and which region constitutes a wild-type regulatory region of the molecule." Applicants traverse this rejection on the grounds that claim 38 is clear and definite. Notwithstanding the foregoing, solely in the interest of expediting examination and in no way acquiescing to the validity of the Examiner's rejections, Applicants have cancelled previously numbered claim 38, thereby rendering rejection of this claim moot. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of the pending claims under 35 U.S.C. § 112, second paragraph.

Rejection of Claims 3, 9-17, 25, 26, 28-34 and 36-38 Under 35 U.S.C. § 112, First Paragraph (Written Description)

The Examiner has rejected claims 3, 9-17, 25, 26, 28-34 and 36-38 under 35 U.S.C. § 112, first paragraph as allegedly "failing to comply with the written description requirement." Applicants respectfully traverse this rejection on the grounds that, based on the teachings in Applicants' specification and the general knowledge in the art at the time of the invention, one skilled in the art would reasonably conclude that Applicants were in possession of the claimed invention at the time the application was filed. In the interest of clarity, Applicants will address each aspect of the Examiner's rejection below.

Rejection of Claims Directed to Allelic Variants

With regard to previously numbered claim 3(c), the Examiner is of the opinion that

> [t]he specification and claims do not indicate what distinguishing attributes are concisely shared by the members of the genera comprising allelic variants of SEQ ID NO:2...nor does the specification describe elements which are essential to various functions claimed for each genus. Concise structural features that could distinguish compounds from others in each broad genus are missing from the disclosure. (Office Action, pages 3-4)

In the interest of expediting examination and in no way acquiescing to the validity of the Examiner's rejection, Applicants have cancelled previously numbered claim 3(c) directed to nucleic acid molecules encoding naturally occurring allelic variants of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, thereby rendering the rejection of this claim, and the claims depending therefrom, moot. Notwithstanding the foregoing, Applicants wish to make the following remarks of record.

Applicants traverse this rejection on the grounds that, based on the teachings of the specification and the state of the art at the time of filing of the present application, one skilled in the art would reasonably conclude that Applicants were in possession of the genus of "naturally occurring variants" of polypeptides comprising SEQ ID NO:2 at the time the application was filed. Applicants direct the Examiner's attention to page 32, lines 4-15 where Applicants define allelic variant as follows:

> In addition to the *C. glutamicum* HA nucleotide sequences shown in Appendix A, it will be appreciated by those of ordinary skill in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequences of HA proteins may exist within a population (*e.g.*, the *C. glutamicum* population). Such genetic polymorphism in the HA gene may exist among individuals within a population due to natural variation... Such natural variations can typically result in 1-5% variance in the nucleotide sequence of the HA gene. Any and all such nucleotide variations and resulting amino acid polymorphisms in HA that are the result of natural variation and do not alter the functional activity of HA proteins are intended to be within the scope of the invention.

Applicants further note that patents, issued at the time of the filing of the present application, describe such naturally occurring variants in a consistent manner. Applicants direct the Examiner's attention to, for example, U.S. Patent No. 5,882,893, issued on March 16, 1999, in which independent claims 1, 14 and 15 are directed to "allelic variants." The specification of U.S. Patent No. 5,882,893 characterizes this term as follows:

> In addition to the mACHR-6 nucleotide sequence shown in SEQ ID NO:1 or 4, it will be appreciated by those skilled in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequences of mACHR-6 may exist within a population (*e.g.*, the human population). Such genetic polymorphism in the mACHR-6 gene may exist among individuals within a population due to natural allelic variation... Such natural allelic variations can typically result in 1-5% variance in the nucleotide sequence of the mACHR-6 gene. Any and all such nucleotide variations and resulting amino acid polymorphisms in mACHR-6 that are the result of natural allelic variation are

> intended to be within the scope of the invention. Such allelic variation includes both active allelic variants as well as non-active or reduced activity allelic variants, the later two types typically giving rise to a pathological disorder. (Column 18, lines 3-32).

In view of the foregoing teachings in Applicants' specification and the art, Applicants submit that a skilled artisan would appreciate that the recitation of a specifically defined nucleotide sequence encoding a polypeptide is representative of the larger genus of nucleic acid molecules encoding naturally occurring allelic variants with similar structure and function. Moreover, Applicants submit that the teachings of the specification with respect to naturally occurring allelic variants sufficiently characterize the structural and functional qualities of allelic variants such that one skilled in the art would conclude that the Applicants were in possession of the claimed naturally occurring allelic variants at the time of filing of the present application.

Rejection of Claims Directed to Sequences of 90% Identity to the Nucleotide Sequence of SEQ ID NO:1

With regard to claim 3(c), directed to nucleotide sequences that are at least 90% identical to SEQ ID NO:1, or a complement thereof, the Examiner is of the opinion that

> the specification fails to teach or adequately describe a representative number of species in each genus such that the common attributes or characteristics concisely identifying members of each proposed genus are exemplified. Since the disclosure fails to describe the common attributes or characteristics concisely identifying members of the proposed genera, and because each genus is highly variant, the description provided for each genus is insufficient. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genera claimed. (Office Action, pages 4-5)

Applicants respectfully traverse this rejection. However, solely in the interest of expediting examination and in no way acquiescing to the validity of the Examiner's rejection, Applicants have amended claim 3(c) to specify that the claimed nucleic acid molecules have a UDP-N-Acetylmuramate-Alanine-Ligase activity.

Applicants would like to direct the Examiner's attention to Example 14 of the *Written Description Guidelines*. This example provides that a claim directed to variants of a protein having SEQ ID NO:3 "that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→B" with an accompanying specification that discloses a single species falling within the claimed genus, satisfies the requirements of 35 U.S.C. §112, first paragraph for written description. The rationale behind the

foregoing conclusion, as presented by the *Written Description Guidelines*, is that "[t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which Applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity." The Guidelines also provide that "[t]he procedures for making variants of SEQ ID NO:3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are conventional in the art."

Similarly, in the present case, claims 3(c), (f) and (h), and claims depending therefrom, are directed to either nucleic acid molecules comprising a nucleotide sequence which is at least 90% identical to SEQ ID NO:1 and which code for polypeptides that have a UDP-N-Acetylmuramate-Alanine-Ligase activity or nucleic acid molecules which code for polypeptides comprising an amino acid sequence which is at least 90% identical to SEQ ID NO:2 and which have a UDP-N-Acetylmuramate-Alanine-Ligase activity. Applicants further note that the specification and the state of the art provide extensive teaching on techniques for designing such sequences and assays for identifying all of the nucleic acid molecules of at least 90% identity to SEQ ID NO:1 which encode a polypeptide having a UDP-N-Acetylmuramate-Alanine-Ligase activity (see, for example, page 34, lines 9-15 of the specification, Examples 4-9 at page 57, line 24 to page 63, line 20 of the specification, and Example 11 at page 64, line 20 to page 66, line 3 of the specification).

The indication in Example 14 of the Written Description Guidelines that the production of polypeptides which contain a ***5% variation from a specific amino acid sequence*** is routine in the art can be equated with the production of nucleic acid molecules which contain a ***10% variation from a specific nucleotide sequence.*** Indeed, the present specification and the general state of the art provide extensive guidance for making and identifying sequences of 90% identity to a specified nucleotide sequence. For example, the specification at page 34, lines 25-27 teaches that conservative substitutions may be made at non-essential amino acid residues of the polypeptide encoded by SEQ ID NO:1, for example, by replacing residues with residues having a similar side chain. Additionally, due to the degeneracy of the genetic code, one skilled in the art will appreciate that numerous nucleotides can be mutated, for example, in the third nucleotide of a codon, without even resulting in a change in the encoded amino acid. Applicants note that a sequence of 90% identity to the nucleotide sequence of SEQ ID NO:1 differs only by about 79 nucleotides from a

sequence of 95% identity to the nucleotide sequence of SEQ ID NO:1. In view of this fact and further in view of the fact that SEQ ID NO:1 encodes a protein of 486 amino acid residues, Applicants submit that one skilled in the art would appreciate that a sequence of 90% identity to SEQ ID NO:1 can be designed without even modifying the sequence of the resulting encoded polypeptide. Indeed, recitation of at least 95% identity in Example 14 is merely exemplary. Similar to the rationale of Example 14, Applicants submit that the disclosed sequence (*i.e.*, SEQ ID NO:1) is representative of the genus of sequences of at least 90% identity to the disclosed sequence and encoding a polypeptide having a UDP-N-Acetylmuramate-Alanine-Ligase activity, particularly in view of the extensive teachings in the specification and the general knowledge in the art.

Accordingly, for at least the foregoing reasons, it would have been clear to one skilled in the art that Applicants were in possession of the claimed invention at the time the application was filed. Applicants, therefore, respectfully request reconsideration and withdrawal of the rejection of claim 3(c), and claims depending therefrom, under 35 U.S.C. § 112, first paragraph as lacking written description.

Rejection of Claims Directed to Nucleic Acid Fragments of at least 15 Contiguous Nucleotides of SEQ ID NO:1 Having a UDP-N-Acetylmuramate-Alanine-Ligase Activity

With regard to previously numbered claim 3(g), the Examiner has asserted that the genus of nucleic acid molecules of at least 15 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:1 which have a UDP-N-Acetylmuramate-Alanine-Ligase activity is not described in the specification such that one skilled in the art would reasonably conclude that Applicants were in possession of the claimed genus at the time of filing.

Applicants respectfully traverse this rejection. However, solely in the interest of expediting examination and in no way acquiescing to the validity of the Examiner's rejection, Applicants have cancelled previously numbered claims 3(f) and 3(g), thereby rendering rejection of the foregoing claims moot.

Rejection of Claims Directed to Host Cells Comprising Nucleic Acid Molecules Having a Modified Regulatory Region

With regard to claim 38, directed to host cells comprising nucleic acid molecules wherein the regulatory region of the nucleic acid molecule is modified relative to the wild-type regulatory region of the molecule, the Examiner is of the opinion that

> [t]he specification does not place any limit on the number of nucleic acid...substitutions, deletions, insertions and/or additions that may be made

> within each genus claimed. Since the disclosure fails to describe the common attributes or characteristics concisely identifying members of the proposed genera, and because each genus is highly variant, the description provided...is insufficient. (Office Action, page 4)

Applicants respectfully traverse the foregoing rejection. However, solely in the interest of expediting examination, but in no way acquiescing to the validity of the Examiner's rejections, Applicants have cancelled claim 38, thereby rendering rejection of the foregoing claim moot.

Rejection of Claims 3, 9-17, 25, 26, 28-34 and 36-38 Under 35 U.S.C. § 112, First Paragraph (Enablement)

The Examiner has rejected claims 3, 9-17, 25, 26, 28-34 and 36-38 under 35 U.S.C. § 112, first paragraph because, according to the Examiner, the specification does not reasonably provide enablement for the claimed invention. Applicants respectfully traverse this rejection and submit that, based on the teachings in Applicants' specification as well as the general knowledge available in the art at the time of the filing of the present application, one of ordinary skill in the art would be able to make and use the claimed invention using only routine experimentation. As an initial matter, solely in order to expedite examination, but in no way acquiescing to the validity of the Examiner's rejection, originally numbered claims 3(c) (directed to nucleic acid molecules encoding allelic variants of a polypeptide comprising the amino acid sequence of SEQ ID NO:2), 3(f) and 3(g) (directed to nucleic acid fragments of SEQ ID NO:1) and 38 (directed to host cells comprising the nucleic acid sequence of SEQ ID NO:1 and, further, a modified regulatory region) have been cancelled, thereby rendering the rejections of these claims moot. Each remaining aspect of the Examiner's rejection is addressed below.

Rejection of Claims Directed to Sequences of 90% Identity to the Nucleotide Sequence of SEQ ID NO:1

With regard to claim 3(c), directed to nucleotide sequences that are at least 90% identical to SEQ ID NO:1, or a complement thereof, the Examiner is of the opinion that

> the specification, while being enabling for in vitro expression of SEQ ID NO:1 in an appropriate microbial host cell, does not reasonably provide enablement for...any isolated nucleic acid molecule comprising at least 90% identity with SEQ ID NO:1. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of the ability to

> modulate production of fine chemicals using a representative number of species of each broadly claimed genus of compounds. (Office Action, pages 5-8)

Applicants respectfully traverse the foregoing rejection. Notwithstanding the foregoing, solely in the interest of expediting examination and in no way acquiescing to the validity of the Examiner's rejection, Applicants have amended claim 3(c) to specify that the claimed nucleic acid molecules have a UDP-N-Acetylmuramate-Alanine-Ligase activity.

Applicants again direct the Examiner's attention to Example 14 of the *Written Description Guidelines*, which states that claims directed to sequences of 95% identity to a disclosed sequence and characterized by a particular function are sufficiently described and enabled in accordance with 35 U.S.C. § 112, first paragraph, where the specification discloses an assay for identifying such sequences. Indeed, the present specification provides extensive guidance for making and identifying such sequences. For example, Applicants have disclosed in the instant specification methods for generating nucleic acid molecules of 90% identity to SEQ ID NO:1 using such techniques as site-directed mutagenesis and PCR-mediated mutagenesis (see, for example, page 34, lines 9-15 of the specification). Applicants submit that such techniques were well known in the art at the time of filing of the instant application, such that one skilled in the art could generate nucleic acid molecules of 90% identity to SEQ ID NO:1 using no more than routine experimentation by following, for example, the protocols set forth by Weiner *et al.*[1], attached herein as Appendix A, or Bauer *et al.*[2], attached herein as Appendix B. In addition, the specification at, for example, page 34, lines 15-27, teaches that conservative substitutions may be made at non-essential amino acid residues of the polypeptide encoded by SEQ ID NO:1, in which an amino acid residue is replaced by a residue having a similar side chain.

Moreover, at page 57, line 24 to page 59, line 10, the specification further elaborates on methods for the *in vivo* mutagenesis of bacterial strains and methods of transferring mutated nucleic acid molecules (*e.g.*, nucleic acid molecules of 90% or 95% identity to the nucleotide sequence of SEQ ID NO:1) into such bacterial strains. In addition, at page 59, line 12 to page 59, line 35, the specification teaches assays for assessing the expression of the mutated molecules in the bacterial strains. At page 61, line 34 to page 62, line 24, the specification teaches assays for assessing the activity of the mutated molecules (*e.g.*, assays for determining whether the mutated protein retains a UDP-N-Acetylmuramate-Alanine-Ligase activity). Furthermore, at page 62, line 26 to page 63, line 20, the specification teaches methods for determining the

[1] Weiner M.P. *et al.*, "Site-directed Mutagenesis using PCR" From *Molecular Biology: Current Innovations and Future Trends*. A.M. Griffin and H.G. Griffin, Eds., (Horizon Scientific Press, 1995)
[2] United States Patent No. 5,789,166

effect of the mutated molecules on the production of a desired product from cultured bacteria. Additionally, at page 64, line 20, to page 66, line 3, the specification teaches techniques for identifying sequence identity, for example, for identifying sequences of at least 90% or 95% identity to SEQ ID NO:1 or SEQ ID NO:2. In view of the foregoing, it is evident that the specification provides extensive teachings that would enable one skilled in the art to design and assess the activity of sequences of 90% or 95% identity to the nucleotide sequence of SEQ ID NO:1 or the amino acid sequence of SEQ ID NO:2.

Applicants submit that, even though Example 14 is part of the *Written Description Guidelines* and not the *Enablement Guidelines*, this example does state explicitly that ***one skilled in the art would be able to generate a nucleotide sequence of 95% identity to another nucleotide sequence using only routine experimentation***. Specifically, the relevant section of Example 14 provides that "*[t]he procedures for making variants of SEQ ID NO:3* ***are conventional in the art*** *and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are* ***conventional in the art***" (**Emphasis added**).

Accordingly, while the *Written Description Guidelines* generally describe the standard for satisfying the written description requirement, in this particular example, the Guidelines clearly provide guidance on the USPTO's position regarding a key question for determining whether the enablement requirement has been satisfied: would it be routine for one of skill in the art to generate a sequence with 90% or 95% identity to a specified nucleotide or amino acid sequence and which retains the activity of that specified nucleotide or amino acid sequence? The answer to that question, as provided by the USPTO, is: yes. The Guidelines provide that claims to sequences of 95% identity with a functional limitation are sufficiently enabled where the specification provides assays for the identification of such sequences having the requisite function. Accordingly, because it is conventional, *i.e.*, routine, to make sequences of at least 90% or 95% identity and because the instant specification provides assays for identifying nucleic acid sequences that encode a polypeptide having a UDP-N-Acetylmuramate-Alanine-Ligase activity (see, for example, Examples 4-9 at page 57, line 24 to page 63, line 20 of the specification and Example 11 at page 64, line 20 to page 66, line 3 of the specification), one of skill in the art would be able to make and use the claimed invention using only routine experimentation.

Lastly, Applicants submit that while Example 14 recites a claim directed to sequences of at least 95% identity to a disclosed sequence, such claim is merely

exemplary. The conclusion that methods for makings sequences of at least 95% identity to a disclosed sequence are conventional in the art does not suggest that sequences of at least 90% to the disclosed sequence are not conventional in the art. Indeed, Applicants submit that, based on the extensive teachings in the specification and the general knowledge in the art, as described above, one skilled in the art would be able to produce sequences of at least 90% identity to the nucleotide sequence of SEQ ID NO:1 which encode polypeptides that retain a UDP-N-Acetylmuramate-Alanine-Ligase activity using only routine experimentation.

Rejection of Claims Directed to Production of Fine Chemicals From Host Cells Comprising Allelic Variants, Fragments of 15 Contiguous Nucleotides of SEQ ID NO:1, Nucleic Acid Molecules Comprising At Least 90% Identity With SEQ ID NO:1, or Nucleic Acid Molecules Having a Modified Regulatory Region

The Examiner is of the opinion that

> the specification, while being enabling for...expression of SEQ ID NO:1 in an appropriate microbial host cell, does not reasonably provide enablement for...methods for the production of fine chemicals from any naturally occurring allelic variant of SEQ ID NO:2, any isolated nucleic acid molecule comprising at least 90% identity with SEQ ID NO:1, any fragment of at least 15 contiguous nucleotides of SEQ ID NO:1 encoding polypeptide having a UDP-N-Acetylmuramate-Alanine-Ligase activity, or any region of SEQ ID NO:1 constituting a modified regulatory region...in relation to the wild-type region of the molecule. (Office Action, page 5)

Applicants respectfully traverse the foregoing rejection for the following reasons.

As an initial matter, Applicants respectfully submit that solely in an effort to expedite examination, but in no way acquiescing to the validity of the Examiner's rejection, originally numbered claims 3(c) (directed to nucleic acid molecules encoding allelic variants of a polypeptide comprising the amino acid sequence of SEQ ID NO:2), 3(f) and 3(g) (directed to nucleic acid fragments of SEQ ID NO:1) and 38 (directed to host cells comprising the nucleic acid sequence of SEQ ID NO:1 and, further, a modified regulatory region) have been cancelled. Accordingly, the rejections of the pending claims as being directed to methods of the production of fine chemicals with respect to these previously claimed nucleic acid variants and host cells have been rendered moot.

With respect to pending claims 3(c)-(j), Applicants initially note that the Examiner, in allowing the method claims as they are directed to pending claims 3(a) and 3(b), has implicitly acknowledged that claims directed to nucleic acid molecules

encoding a polypeptide having a UDP-N-Acetylmuramate-Alanine-Ligase activity are enabled. Indeed, the Examiner has implicitly acknowledged that UDP-N-Acetylmuramate-Alanine-Ligase activity is involved in the production of fine chemicals. Accordingly, Applicants note that solely in the interest of expediting examination and in no way acquiescing to the validity of the Examiner's rejections, Applicants have amended claims 3(c)-(j) to specify that the claimed variants of SEQ ID NO:1 and 2 each have a UDP-N-Acetylmuramate-Alanine-Ligase activity. As such, one skilled in the art would appreciate that such claimed nucleic acid molecules, although variants of SEQ ID NOs:1 and 2, each possess UDP-N-Acetylmuramate-Alanine-Ligase activity and, therefore, can be used to modulate the production of fine chemicals.

Moreover, it was known in the art at the time of filing of the instant application that UDP-N-Acetylmuramate-Alanine-Ligase performs an essential function in cell wall biogenesis by catalyzing the formation of an amide bond between UDP-N-acetylmuramic acid (UDP-MurNAc) and L-alanine, one of the initial steps in peptidoglycan synthesis.[3] Furthermore, as taught in the specification, modulation of the expression of proteins involved in cell wall construction can affect the yield, production, and/or efficiency of production of a fine chemical in a host cell by, for example, allowing the cell to withstand mechanical and other stresses present during large-scale fermentative culture, or allowing increased growth rates of the microorganisms producing a desired fine chemical (see page 4, lines 1-12 and 32-34 of the specification; see also page 20, line 30 to page 22, line 6 of the specification). As further taught in the specification (see page 4, lines 1-12 and 32-34 of the specification; see also page 20, line 30 to page 22, line 6 of the specification), large scale fermentative culture requires significant cell wall production. Accordingly, based on the teachings in the specification and the general knowledge in the art at the time of filing, one skilled in the art would appreciate that modulation of the activity and/or expression of UDP-N-Acetylmuramate-Alanine-Ligase can serve to modulate, for example, enhance the production of fine chemicals.

Moreover, Applicants submit that the specification teaches how one of skill in the art can use the claimed variants encoding polypeptides having UDP-N-Acetylmuramate-Alanine-Ligase to modulate the production of fine chemicals. As indicated above, Examples 4-10, at page 57, line 24 to page 64, line 18 of the specification, teach methods for generating the claimed variants in bacteria, *e.g.*, *Corynebacterium glutamicum*, methods of culturing the bacteria, culture conditions and methods of collecting the desired fine chemical from the culture. Additionally,

[3] See Bouhss *et al.* (*Biochemistry* (1997) 36:11556-11563) and Liger *et al.* (*Microbial Drug Resistance* (1996) 2(1):25-27), attached herewith as Appendices C and D.

the specification, at least in Example 5, describes how sequences of the invention may be manipulated, for example, mutagenized, overexpressed or underexpressed, to optimize production of a desired fine chemical such as lysine. Standard techniques known in the art, for example, the use of plasmid or viral vectors to transform *Corynebacterium glutamicum*, may be utilized to engineer a desired bacterium to enhance production of fine chemicals, as taught at page 37, line 14 to page 44, line 19 of the specification. The specification provides extensive teachings regarding methods for transfection of host cells with the nucleic acid molecules of the invention (see, for example, page 42, line 23 to page 43, line 9 of the specification). Moreover, the specification, at least in Example 9, describes how techniques such as spectroscopy, thin layer chromatography, and high performance liquid chromatography, may be used to determine whether engineered mutant proteins have the desired effect on fine chemical production within a host bacterium. The specification further describes, in Example 7, media and culture conditions so as to optimize fine chemical production. Moreover, the specification, at least in Example 10, describes how fine chemicals may be recovered (for example, by natural secretion from the cells or centrifugation), purified (for example, by chromatographic techniques) and concentrated (for example, by filtration or ultrafiltration). Accordingly, the specification provides extensive teachings to instruct one of skill in the art how to produce fine chemicals using the nucleic acid and polypeptide molecules of the present invention without undue experimentation.

For each of the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of the pending claims under 35 U.S.C. § 112, first paragraph.

Rejection of Claims Directed to a Method for Diagnosing the Presence or Activity of Corynebacterium diphtheriae *in a Subject*

With regard to claim 35, directed to methods of diagnosing the presence of *Corynebacterium diphtheriae* in a subject, the Examiner is of the opinion that "Applicants have not provided guidance in the specification toward methods of...diagnosis of any infections in a subject" (Office Action, pages 6-7).

Applicants respectfully traverse this rejection. Applicants submit that, based on the teachings in the specification and the general knowledge in the art, one skilled in the art would be able to diagnose the presence or activity of *Corynebacterium diphtheriae* in a subject using the claimed nucleic acid molecules of the invention with no more than routine experimentation. However, solely in the interest of expediting examination, but in no way acquiescing to the validity of the Examiner's rejections, Applicants have cancelled claim 35, thereby rendering this rejection as it pertains to claim 35 moot.

In view of the foregoing teachings in the specification and the general knowledge in the art at the time of filing of the present application, one of skill in the art would be able to make and use the claimed invention using only routine experimentation. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of the pending claims under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 3, 9-13, 15-17, 25 and 30-33 Under 35 U.S.C. § 102(b)

The Examiner has rejected claims 3, 9-13, 15-17, 25 and 30-33 under 35 U.S.C. § 102(b) as being anticipated by Smith *et al.* (USPN 5,871,960; hereinafter referred to as "Smith"), Kobayashi *et al.* (Accession No. AB003132; hereinafter "Kobayashi") and Wachi *et al.* (Accession No. AB015023; hereinafter "Wachi"). In particular, the Examiner is of the opinion that each of these references "teach isolated microbial host cells and expression vectors expressing nucleic acids encoding fragments of SEQ ID NO:1."

As an initial matter, with respect to Wachi, Applicants submit that according to the sequence revision history provided by NCBI, as set forth herein as Appendix E, the earliest publication of the sequence provided by Wachi was November 13, 1998, not May 27, 1998 as asserted by the Examiner. Accordingly, Applicants submit that Wachi constitutes prior art under 35 U.S.C. § 102(a), not prior art under 35 U.S.C. § 102(b).

Nonetheless, Applicants traverse the foregoing rejection for the following reasons. For a prior art reference to anticipate, in terms of 35 U.S.C. § 102, a claimed invention, the prior art must teach each and every element of the claimed invention. *Lewmar Marine v. Barient*, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987). As indicated above, claim 3, as amended, is directed to (a) an isolated nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1, or a full complement thereof; (b) an isolated nucleic acid molecule which encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:2, or a full complement thereof; (c) an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 90% identical to the entire nucleotide sequence of SEQ ID NO:1, or a full complement thereof, wherein the nucleic acid molecule encodes a polypeptide having a UDP-N-Acetylmuramate-Alanine-Ligase activity, and wherein said nucleic acid molecule comprises less than 0.5 kb of nucleotide sequences which naturally flank the nucleotide sequence of SEQ ID NO:1; (d) an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the entire nucleotide sequence of SEQ ID NO:1, or a full complement thereof, wherein the nucleic acid molecule encodes a polypeptide having a UDP-N-Acetylmuramate-

Alanine-Ligase activity, and wherein said nucleic acid molecule comprises less than 0.5 kb of nucleotide sequences which naturally flank the nucleotide sequence of SEQ ID NO:1; (e) an isolated nucleic acid molecule which hybridizes to the complement of the nucleotide sequence of SEQ ID NO:1 in 6X sodium chloride/sodium citrate (SSC) at 45°C, followed by one or more washes in 0.2 X SSC, 0.1% SDS at 50-65°C or a full complement thereof wherein said nucleic acid molecule encodes a polypeptide having a UDP-N-Acetylmuramate Alanine-Ligase activity and comprises less than 0.5 kb of nucleotide sequences which naturally flank the nucleotide sequence of SEQ ID NO:1; (f) an isolated nucleic acid molecule which encodes a polypeptide comprising an amino acid sequence which is at least 90% identical to the entire amino acid sequence of SEQ ID NO:2, or a full complement thereof, wherein said nucleic acid molecule encodes only a protein having a UDP-N-Acetylmuramate-Alanine-Ligase activity; (g) an isolated nucleic acid molecule which encodes a polypeptide comprising an amino acid sequence which is at least 95% identical to the entire amino acid sequence of SEQ ID NO:2, or a full complement thereof, wherein said nucleic acid molecule encodes only a protein having a UDP-N-Acetylmuramate-Alanine-Ligase activity; (h) an isolated nucleic acid molecule which comprises a nucleotide sequence which is at least 90% identical to the entire nucleotide sequence of SEQ ID NO:1, or a full complement thereof, wherein said nucleic acid molecule encodes only a protein having a UDP-N-Acetylmuramate-Alanine-Ligase activity; (i) an isolated nucleic acid molecule which comprises a nucleotide sequence which is at least 95% identical to the entire nucleotide sequence of SEQ ID NO:1, or a full complement thereof, wherein said nucleic acid molecule encodes only a protein having a UDP-N-Acetylmuramate-Alanine-Ligase activity; and (j) an isolated nucleic acid molecule which hybridizes to the complement of the nucleotide sequence of SEQ ID NO:1 in 6X sodium chloride/sodium citrate (SSC) at 45°C, followed by one or more washes in 0.2 X SSC, 0.1% SDS at 50-65°C or a full complement thereof, wherein said nucleic acid molecule encodes only a polypeptide having a UDP-N-Acetylmuramate-Alanine-Ligase activity.

Applicants respectfully submit that Smith, Kobayachi, and Wachi each fail to teach or suggest each and every element of the claimed invention. Specifically, Applicants respectfully submit that neither Smith, nor Kobayachi nor Wachi disclose a nucleic acid molecule comprising SEQ ID NO:1 or a nucleic acid molecule encoding SEQ ID NO:2.

Moreover, Applicants respectfully submit that, as evidenced by the alignments presented herein as Appendices F-H,[4] Smith, Kobayachi and Wachi, alone or in

[4] A global alignment of SEQ ID NO:1 of the present application versus SEQ ID NO:30 of Smith is attached herein as Appendix F; a global alignment of SEQ ID NO:1 of the present application versus the nucleotide sequence of Kobayachi is attached herein as Appendix G; and a global alignment of

combination, fail to teach or suggest a nucleic acid molecule of 90% or 95% identity to SEQ ID NO:1, or a nucleic acid molecule which hybridizes under highly stringent hybridization conditions to the complement of the nucleotide sequence of SEQ ID NO:1, wherein the nucleic acid molecule comprises ***less than 0.5 kb of nucleotide sequences which naturally flank the nucleotide sequence of SEQ ID NO:1***.

Applicants further submit that Smith, Kobayachi and Wachi each fail to teach or suggest an isolated nucleic acid molecule which encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:2, ***wherein the nucleic acid molecule encodes only a protein having a UDP-N-Acetylmuramate-Alanine-Ligase activity***. With respect specifically to Kobayachi, Applicants direct the Examiner's attention to Kobayachi *et al.*,[5] Biochem. Biophys. Res. Commun. (1997) 236:383-388 and, further, to GenBank Accession No. AB003132[6], which indicate that the nucleic acid molecule of Kobayachi contains five open reading frames encoding ***at least three polypeptides***. With respect specifically to Wachi, Applicants direct the Examiner's attention to Wachi *et al.*,[7] Appl. Microbiol. Biotechnol. (1999) 51:223-228 and, further, GenBank Accession No. AB015023[8], which sets forth that the nucleic acid molecule of Wachi would encode ***at least two polypeptides***. Applicants further submit that, as evidenced by the alignment submitted herewith as Appendix F, Smith teaches a fragment of only five contiguous nucleotides of the nucleic acid molecule of SEQ ID NO:1, and therefore does not teach or suggest a nucleic acid molecule that encodes a polypeptide having a UDP-N-Acetylmuramate-Alanine-Ligase activity.

Accordingly, Smith, Kobayachi and Wachi fail to anticipate the claimed invention, and Applicants respectfully request reconsideration and withdrawal of this rejection of the pending claims under 35 U.S.C. § 102(b).

SEQ ID NO:1 of the present application versus the nucleotide sequence of Wachi is attached herein as Appendix H.

[5] For the Examiner's convenience, a copy of the cited reference is attached herein as Appendix I.

[6] For the Examiner's convenience, a copy of the cited reference is attached herein as Appendix J.

[7] For the Examiner's convenience, a copy of the cited reference is attached herein as Appendix K.

[8] For the Examiner's convenience, a copy of the cited reference is attached herein as Appendix L.

CONCLUSION

In view of the foregoing remarks, reconsideration of the rejections and allowance of all pending claims is respectfully requested. If there are any remaining issues or if the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

The Commissioner is hereby authorized to charge any deficiency in the fees paid herewith, or credit any overpayment, to Deposit Account No. 12-0080, under Order No. BGI-132CPCN, from which the undersigned is authorized to withdraw.

Dated: **September 24, 2007**

Respectfully submitted,

By _____

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